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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CALAMITA, HEATHER	
ART UNIT	**PAPER NUMBER**
1637	

DATE MAILED: 05/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,383	NALLUR ET AL.	
	Examiner	Art Unit	
	Heather G. Calamita, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62 and 68-75* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-62 and 68-75* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. Amendments of March 14, 2005 have been received and entered in full. Claims 1-62 and 68-75 are pending and under examination. Any objections and rejections not reiterated below are hereby withdrawn.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-17, 18-29, 31-47, 53-58, 61, 62, 68 and 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (USPN 6,316,229 B1 11/13/2001) in view of Lizardi (US 2003/0032024 A1 02/13/2003).

Lizardi et al. teach (claims 1, 53, 56, 62, 68 and 70-72) a method of amplifying messenger RNA, the method comprising (see entire document, specifically col. 42 line 13)

(a) mixing one or more RT primers with a nucleic acid sample and reverse transcribing to produce CDNA strands each comprising one of the RT primers, wherein each RT primer comprises a reverse transcription primer portion (see col. 77 line 2). Lizardi et al. indicate RNA can be used with the methodologies disclosed.

(b) mixing the cDNA strands with a set of capture probes under conditions that promote hybridization of the CDNA strands to the capture probes (see col. 42 lines 27-52),

(c) mixing one or more rolling circle replication primers with the cDNA strands under conditions that promote association of the cDNA strands with the rolling circle replication primers, wherein the rolling

circle replication primers each comprise a capture tag, wherein the association occurs via the capture tag (see col. 42 lines 27-52),

(d) mixing one or more amplification target circles with the rolling circle replication primers under conditions that promote association of the rolling circle replication primers with the amplification target circles (see col. 42 lines 53-67),

(e) incubating the amplification target circles under conditions that promote replication of the amplification target circles(see col. 42 lines 65-67, col. 43 lines 1-4), wherein replication of the amplification target circles results in the formation of tandem sequence DNA (see col. 43 lines 5-20).

With regard to claim 2, Lizardi et al. teach the capture tag associates with the RT primer (see col. 48 liens 24-37 and col. 77 line 57).

With regard to claim 3, Lizardi et al. teach the reverse transcription primer portion of each RT primer comprises poly T (see col. 77 line 65).

With regard to claim 4, Lizardi et al. teach the capture probes are immobilized on a substrate (see col. 42 lines 29-30).

With regard to claim 5, Lizardi et al. teach the capture probes are in an array (see col. 42 line 8).

With regard to claim 6, Lizardi et al. teach the capture probes are immobilized via a capture tag coupled to the capture probes (see example 5 col. 78 steps 1 and 2).

With regard to claim 7, Lizardi et al. teach each capture probe comprises a sequence matching all or a portion of the sequence of messenger RNA molecules of interest (see col. 77 line 65, col. 78 line 4).

With regard to claims 8-12, Lizardi et al. teach the set of capture probes collectively comprise sequence matching all or a portion of the sequence of a plurality of different messenger RNA molecules associated with a disease from a source of interest (see col. 51 lines 63-67, col. 52 lines 1-40).

With regard to claim 13, Lizardi et al. teach the ends of the capture probes are extendable when a cDNA strand is hybridized to the capture probe (see col. 42 line 67).

With regard to claim 14, Lizardi et al. teach the ends of the capture probes are designed to be extendable only when a CDNA strand corresponding to a particular form of a messenger RNA of interest is hybridized to the capture probe (see col. 42 line 67).

With regard to claim 15, Lizardi et al. teach the ends of the capture probes are not extendable by polymerase (see col. 47 lines 62-64).

With regard to claim 18, Lizardi et al. teach further comprising, simultaneous with, or following, step (d), mixing a secondary DNA strand displacement primer with the amplification target circles and incubating under conditions that promote hybridization between the tandem sequence DNA and the secondary DNA strand displacement primer and replication of the tandem sequence DNA, wherein replication of the tandem sequence DNA results in the formation of secondary tandem sequence DNA (see col. 55 lines 40-54).

With regard to claim 19, Lizardi et al. teach further comprising, simultaneous with step (e), mixing a tertiary DNA strand displacement primer with the amplification target circles (see col. 55 lines 1-10).

With regard to claim 20, Lizardi et al. teach further comprising detecting the tandem sequence DNA, wherein detection of tandem sequence DNA indicates that the corresponding messenger RNA molecule was present in the nucleic acid sample (see col. 52 lines 5-27).

With regard to claim 21, Lizardi et al. teach the tandem sequence DNA is detected while in association with the capture probes.

With regard to claim 22, Lizardi et al. teach the identity of the capture probe associated with a tandem sequence DNA indicates the identity of the corresponding messenger RNA molecule (see col. 52 lines 5-27).

With regard to claim 23, Lizardi et al. teach the tandem sequence DNA is detected at the site where the capture probe is located, and wherein the location of the capture probe indicates the identity of the corresponding messenger RNA molecule (see col. 52 lines 5-27).

With regard to claim 24, Lizardi et al. teach detection is mediated by detection probes or by a detection label incorporated in the tandem sequence DNA (see col. 48 lines 48-54).

With regard to claim 25, Lizardi et al. teach the detection label is a ligand (see col. 48 line 47). With regard to claim 26, Lizardi et al. teach the ligand is Brdu (see col. 48 lines 32-33).

With regard to claim 27, Lizardi et al. teach the ligand is Brdu, wherein the tandem sequence DNA is detected by associating an anti-Brdu antibody with the tandem sequence DNA and detecting the antiBrdu antibody (see col. 48 line 33).

With regard to claim 28, Lizardi et al. teach the anti-Brdu antibody comprises a label, wherein the anti-Brdu antibody is detected by detecting the label (see col. 48 lines 32-33).

With regard to claim 29, Lizardi et al. teach the label on the anti-Brdu antibody is a fluorophore (see col. 48 lines 32-37).

With regard to claim 31, Lizardi et al. teach further comprising mixing a set of detection probes with the tandem sequence DNA under conditions that promote hybridization between the tandem sequence DNA and the detection probes, and detecting a plurality of different sequences present in the tandem sequence DNA (see col. 61 lines 9-21).

With regard to claim 32, Lizardi et al. teach the tandem sequence DNA is collapsed using collapsing probes (see col. 52 lines 60-67).

With regard to claim 33, Lizardi et al. teach at least one of the collapsing probes is a collapsing detection probe (see col. 52 lines 22-23, 60).

With regard to claim 34, Lizardi et al. teach the tandem sequence DNA is collapsed by mixing the collapsing probes with the tandem sequence DNA, and incubating under conditions that promote

hybridization between the collapsing probes and the tandem sequence DNA (see col. 52 lines 66-67, col. 55 line 14).

With regard to claim 35, Lizardi et al. teach further comprising, prior to or simultaneous with the mixing of the collapsing probes with the tandem sequence DNA, mixing detection probes with the tandem sequence DNA, and incubating under conditions that promote hybridization between the detection probes and the tandem sequence DNA (see col. 62 lines 66-67, col. 63 lines 1-10).

With regard to claim 36, Lizardi et al. teach the collapsing probes comprise ligands, haptens, or both coupled to or incorporated into oligonucleotides (see col. 63 lines 50-53, col. 24 lines 65-67).

With regard to claim 37, Lizardi et al. teach the RT primer comprises a capture tag (see col. 23 lines 50-67).

With regard to claim 38, Lizardi et al. teach the capture tag on the RT primer is selected from the group consisting of biotin, digoxigenin, bromodeoxyuridine, or other hapten (see col. 23 lines 50-67).

With regard to claim 39, Lizardi et al. teach the cDNA strands comprise capture tags (see col. 23 lines 50-67).

With regard to claim 40, Lizardi et al. teach the cDNA strands comprise capture tags (see col. 23 lines 50-67).

With regard to claim 41, Lizardi et al. teach the capture tags on the cDNA strands are selected from the group consisting of biotin, digoxigenin, bromodeoxyuridine, or other hapten (see col. 23 lines 50-67). With regard to claim 42, Lizardi et al. teach the association is covalent (see col. 48 line 28).

With regard to claims 43 and 44, Lizardi et al. teach the association occurs between a protein and a nucleic acid (see col. 78 lines 31-32).

With regard to claim 45, Lizardi et al. teach the association occurs between two proteins (see col. 78 lines 32-33).

With regard to claim 46, Lizardi et al. teach the capture tags on the cDNA strands are biotin (see col. 53 lines 53-57).

With regard to claim 47, Lizardi et al. teach the capture tags on the rolling circle replication primers comprise antibodies that bind biotin (see col. 53 lines 53-57).

With regard to claims 54 and 57, Lizardi et al. teach the rolling circle replication primers each comprise a capture tag (see col. 43 lines 10-20).

With regard to claims 55 and 58, Lizardi et al. teach association of the rolling circle replication primers with the cDNA occurs via association of the capture tag added to the cDNA and the capture tag in the rolling circle replication primers (see col. 43 lines 10-20).

With regard to claim 61, Lizardi et al. teach the capture tag is derived from incorporation of biotinylated-ddNTP into the cDNA (see col. 43 lines 10-20).

Lizardi et al. do not teach the capture tag is an antibody. Lizardi et al. do not teach mixing one or more half probes with the cDNA strands wherein each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating half probes and capture probes hybridized. Lizardi do not teach following ligation, incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe.

Lizardi (US 2003/0032024 A1 02/13/2003) teaches the capture tag is an antibody (see paragraph 0019 lines 19-22). With regard to claims 16 and 17, Lizardi teaches mixing one or more half probes (gap oligonucleotides) with the cDNA strands wherein each half probe is designed to hybridize to a cDNA strand adjacent to where a capture probe hybridizes, ligating the half probes and capture probes hybridized, and after ligation , incubating the capture probes at a temperature above the melting temperature of the capture probe but below the melting temperature of the ligated capture probe/half probe (see paragraph 0195).

One of ordinary skill in the art at the time the invention was made one would have been motivated to apply Gap oligonucleotides as taught by Lizardi (US 2003/0032024 A1 02/13/2003) to the method of amplifying target nucleic acids as taught by Lizardi et al.(USPN 6,316,229 B1 11/13/2001) in order to achieve more selective target discrimination. Lizardi (US 2003/0032024 A1 02/13/2003) states using gap oligonucleotides enhance target dependency in LCR and this can be adapted for use in LM-RCA, and this method enhances target discrimination. It would have been prima facie obvious to use the gap oligonucleotide as taught by Lizardi (US 2003/0032024 A1 02/13/2003) the method of amplifying nucleic acids as taught by Lizardi et al. (USPN 6,316,229 B1 11/13/2001) in order to achieve the expected advantage of enhancing target nucleic acid discrimination.

3. Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (USPN 6,316,229 B1 11/13/2001) in view of Lizardi (US 2003/0032024 A1 02/13/2003) and in further view of Waggoner et al. (USPN 6,008,373 12/28/1999).

The teachings of Lizardi et al. (229) and Lizardi (024) are described previously.

Neither Lizardi et al. (229) nor Lizardi (024) teach phycoerythrin as a fluorophore.

Waggoner et al. teach using phycoerythrin as a fluorophore in the detection label on an antibody (see col. 21 line 64).

One of ordinary skill in the art at the time the invention was made one would have been motivated to use phycoerythrin as taught by Waggoner et al. (USPN 6,008,373 12/28/1999) with the method of amplifying target nucleic acids as taught by Lizardi et al.(USPN 6,316,229 B1 11/13/2001) to achieve a detection signal that provides fluorescence that is relatively free of interference from other biological materials and provides a multicolor fluorescence emission using a single wavelength excitation. Waggoner et al. (USPN 6,008,373 12/28/1999) states that phycoerythrin is advantageous because it is low molecular weight and provides a multicolor fluorescence emission using a single

wavelength excitation (see col. 2 lines 28-30). It would have been prima facie obvious to use Phycoerythrin as taught by Waggoner et al. (USPN 6,008,373 12/28/1999) with the method of amplifying nucleic acids as taught by Lizardi et al.(USPN 6,316,229 B1 11/13/2001) in order to achieve the expected advantage of a label that has a low molecular weight and provides a multicolor fluorescence emission from a single excitation wavelength.

4. Claims 48-52, 69 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al. (USPN 6,316,229 B1 11/13/2001) in view of Lizardi (US 2003/0032024 A1 02/13/2003) and in further view of Cao et al. (US 2002/0120409 A1 08/29/2002).

The teachings of Lizardi et al. (229) and Lizardi (024) are described previously.

Neither Lizardi et al. (229) nor Lizardi (024) teach fragmenting and labeling cDNA strands to form labeled fragmented cDNA.

Cao et al. teach fragmented cDNA in a method to amplify mRNA (see claim 1 page 8).

One of ordinary skill in the art at the time the invention was made one would have been motivated to apply the method of fragmenting and labeling cDNA as taught by Cao et al. (US 2002/0120409 A1 08/29/2002) to the method of amplifying target nucleic acids as taught by Lizardi et al.(USPN 6,316,229 B1 11/13/2001) to obtain labeled cDNA fragments that are used in assessing gene expression. It would have been prima facie obvious to apply fragmenting and labeling cDNA as taught by Cao et al. (US 2002/0120409 A1 08/29/2002) to the method of amplifying target nucleic acids as taught by Lizardi et al.(USPN 6,316,229 B1 11/13/2001) in order to achieve the expected advantage of using the labeled cDNA fragments in gene expression arrays.

5. Claims 59-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lizardi et al.(USPN 6,316,229 B1 11/13/2001) in view of Lizardi (US 2003/0032024 A1 02/13/2003) and in further view of Shoemaker et al. (USPN 6,713257 B2 03/30/2004).

The teachings of Lizardi et al. (229) and Lizardi (024) are described previously.

Neither Lizardi et al. (229) nor Lizardi (024) teach a capture tag derived from allyl amine dUTP.

Shoemaker et al. teaches using an amino-allyl dUTP in labeling cDNA (see col. 34 line 8).

One of ordinary skill in the art at the time the invention was made one would have been motivated to the method of labeling cDNA as taught by Shoemaker et al. (USPN 6,713257 B2 03/30/2004) to the method of amplifying target nucleic acids as taught by Lizardi et al.(USPN 6,316,229 B1 11/13/2001) to obtain labeled cDNA that are used in assessing gene expression. It would have been prima facie obvious to use the method of labeling cDNA as taught by Shoemaker et al. (USPN 6,713257 B2 03/30/2004) with the method of amplifying target nucleic acids as taught by Lizardi et al. (USPN 6,316,229 B1 11/13/2001) in order to achieve the expected advantage of incorporating a detectible fluorescent label into the cDNA of interest.

Response to Arguments

6. Applicants' arguments filed March 14, 2005, have been fully considered but they are not persuasive.

With respect to claims 1-15, 18-29, 31-47, 56-58, 61, 68 and 71, Applicant's arguments are moot in view of the new ground(s) of rejection.

With respect to claims 37-39, 53-55, 62, 70 and 72, Applicant argues Lizardi et al. (USPN 6,316,229) fail to specifically to RT primers. Applicant further argues Lizardi et al. (299) fail to disclose the RT primers used to produce the cDNA comprise capture tags and the association between the rolling circle replication primers and the cDNA occurs via the capture tags. Lizardi et al. (299) teaches that RNA can be used with the methodoligies disclosed. Lizardi et al. (299) teach cDNA which inherently requires

the use of RT primers. With respect to the capture tag comprising an antibody as recited in the amended claims has been addressed with the new 103 (a) rejections.

Conclusion

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Heather G. Calamita whose telephone number is 571.272.2876 and whose e-mail address is heather.calamita@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route. The examiner can normally be reached on Monday through Thursday, 7:00 AM to 5:30 PM.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Gary Benzion can be reached at 571.272.0782.

Papers related to this application may be faxed to Group 1637 via the PTO Fax Center using the fax number 571.273.8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to 571.272.0547.

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hgc

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5/11/5